REMARKS

Reconsideration of the present application is respectfully requested for the reasons that follow.

October 28, 2008 Examiner Interview

Applicants wish to thank Examiners Gupta and Niebauer for the in-person interview that took place on October 28, 2008. Applicants acknowledge the Interview Summary that was received at the conclusion of the interview. Applicants appreciate the Examiners' willingness to consider the additional evidence of the state of the art that was discussed during the interview and which is presented herewith, including the March et al. 2004 paper, and the DeMartino et al., 1995 paper. As we discussed during the interview, and as is explained hereinbelow, the state of the art as of applicants' earliest filing date, as evidenced by these two papers, taught a person of ordinary skill in the art that a human C5a receptor modulator required an arginine in the N-terminal position in order to exhibit affinity for the receptor. In short, applicants' representatives and the Examiners discussed the standing obviousness rejection in view of the Kawai reference cited in the July 30, 2008 Office Action. In addition, there was a discussion of evidence that could support a finding of non-obviousness. This evidence and the position it supports is set out herein.

35 U.S.C. § 103(a) Rejection

The Examiner has rejected claims 125-126 under 35 U.S.C. § 103(a) as being obvious over Kawai (U.S. Patent No. 5,387,671). Kawai does not teach an embodiment or specific example of the elected species. However, the Examiner argues that the examples in Kawai, when considered as a whole, render the compounds of claims 125 and 126 obvious and that the elected species falls within the genus of claim 1 of Kawai.

In response, applicants respectfully traverse the rejection. An obviousness analysis must take into consideration the state of the art at the time as prescribed by Graham (Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)). In addition, the fact that the elected species may fall within a genus disclosed in the prior art, does not per se render that species obvious over the prior art (see In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992)). Rather, a prima facie case of obviousness must still be established using the Graham factors, as in any other obviousness analysis. If the Examiner establishes a prima facie case of obviousness using this analysis, this finding can still be overcome by a showing of unexpected results (see MPEP § 2144.08).

The compound of claims 125-126 requires two structural features (e.g., Hoo at C-terminal end and Arg at N-terminus) that are different from and not taught or suggested by the genus of compounds disclosed in Kawai. The state of the art also teaches away from the structural requirements of the claimed compound (see March et al. 2004 and DeMartino et al., 1995). Finally, applicants have previously submitted experimental evidence which supports the non-obviousness of the claimed compound. Taken together, the evidence supports a finding of non-obviousness and applicants request the Examiner to reconsider.

In particular, the first difference between the claimed compound and Kawai relates to the terminal Hoo residue recited in instant claims. Hoo is hydroorotic acid, which is a hydrated substituted pyrimidine (see specification, p. 79). In contrast, the corresponding terminal end of the Kawai oligopeptide is identified by position A which is defined as an aryl group (R_1 alone, or R_1 and R_2 together). Kawai defines an aryl group as a substituted or unsubstituted carbocyclic aromatic group (Kawai, col. 13, ll. 15-16). Therefore, the Hoo residue of instant claim 125 is not encompassed by the Kawai definition. In addition, Kawai does not teach or suggest that position A can be substituted with a heterocycle. Furthermore, one of ordinary skill in the art would not consider replacing an aryl group with a substituted pyrimidine and expect it to have similar or improved properties. Therefore, one of skill in the art would not have been

motivated to select the claimed compound. For these reasons, a person of ordinary skill in the art would not have found the claimed invention obvious in view of the teachings of Kawai.

The second difference between the teaching of Kawai and the claimed compound relates to the terminal Phe required by claims 125-126 at the amino-terminus. The art taught one to place an arginine at the N-terminus of such a compound, not a Phe. In particular, Kawai teaches that a polar and charged arginine group is required to be present to achieve significant antagonistic activity. This teaching of Kawai is consistent with other references that make up the state of the art. Papers published contemporaneously with the filing of the patent application, also teach away from modifying the terminal arginine group. For instance, March et al. teach that a terminal arginine is critical for binding affinity to a human C5a receptor and is present in all of its analogs (March et al., *Potent Cyclic Antagonists of the Complement C5a Receptor on Human Polymorphonuclear Leukocytes. Relationships Between Structures and Activity*, 65 Mol. Pharmacol. 868, 875 (2004)). March et al. disclose that the terminal arginine is a likely determinant of receptor affinity. Thus, March et al. teach that without the terminal arginine, an oligopeptide will not be able to bind to the C5a receptor, and would therefore not be a useful modulator. Indeed, this arginine requirement was taught in the art by DeMartino et al. in 1995. The DeMartino et al. paper discloses that a terminal arginine is required in order for a peptide to exhibit binding affinity for the human C5a receptor. (DeMartino et al., *Arginine 206 of the C5a Receptor is Critical for Ligand Recognition and Receptor Activation by C-terminal Hexapeptide Analogs*, 270 J. Biol. Chem. 15966, 15966 (1995)). Thus, the state of the art at the time would have taught a person of ordinary skill in the art that a required structural feature of a peptide modulator of human C5a receptor is an N-terminal arginine. Kawai is consistent with these teachings in that the vast majority of species disclosed have an N-terminal arginine.

In contrast, the compound of claims 125-126 is characterized by the presence of a hydrophobic side chain on its N-terminal which, in contrast to Kawai examples 170

and 171, provides effective C5a antagonistic activity having an IC50 value of less than 200 nM. Furthermore, of the 20 peptides described in Kawai along with their IC50 values (for binding to C5aR), 19 feature a terminal arginine. The peptides containing arginine are reported to have a binding affinity of as low as 0.014 μM (Kawai, Table 1). Only one peptide holds a C-terminal phenylbutanoyl residue which could interact via hydrophobic interactions. This peptide (Kawai, example 170), however, is reported to have an IC50 value of only 2.6 μM. Finally, a person of ordinary skill in the art at the time would read the teachings of Kawai as a whole, and against the backdrop of the existing state of the art. A person reading Kawai would see the genus disclosed is large, indeed, the genus of compounds disclosed in Kawai includes over one trillion possible members. Nothing in Kawai would lead one of ordinary skill in the art to select a compound out of those trillion possibilities that is structurally similar to the claimed compound. This is especially true when a person of ordinary skill in the art is taught away from the claimed compound structure by the long-standing knowledge in the art that an arginine at the N-terminus is needed for binding to human C5a receptor. Therefore, one of skill in the art would not have been motivated to create the compound of claims 125-126.

Even assuming arguendo, that a prima facie case of obviousness has been established, Applicants have rebutted that showing by submitting data showing that the compound of claims 125-126 has unexpected antagonistic properties when compared to the compound of Example 171 in Kawai, which the Examiner had indicated during the interview has the closest structural similarity. The results are shown in the Rule 132 Declaration submitted previously. The compound of Kawai example 171 has an activity in a functional binding assay of > 19 μM, whereas the compound of claims 125-126 has an activity of 0.039 μM in the same assay. It is clear that the difference in antagonistic activity is an unexpected improvement and a sufficient showing of non-obviousness.

In light of the fact that the compound of claims 125-126 has at least two non-obvious structural features when compared with the teachings of Kawai and the state of

the art, the Examiner's position with respect to a prima facie showing of obviousness is clearly overcome. In addition, applicants have further rebutted the obviousness rejection with a Declaration demonstrating unexpected properties of the claimed compound when compared to the most similar compound in the Kawai disclosure. In view of the evidence set out above, applicants respectfully request the Examiner to reconsider and withdraw this rejection, and allow the application to issue as a patent.

Provisional Obviousness-Type Double Patenting Rejection

The Examiner has provisionally rejected claims 125 and 126 under the judicially created doctrine of obviousness-type non-statutory double patenting as being unpatentable over claims 24, 44 of co-pending Application No. 11/814,050. This is a provisional rejection because the conflicting claims have not in fact been patented. In view of the evidence and discussion above, applicants believe this application to be condition for allowance, and accordingly request the Examiner to withdraw this provisional rejection, and allow this application to issue as a patent.

In view of the foregoing, it is submitted that the present application is now in condition for allowance. Reconsideration and allowance of the pending claims are requested. The Director is authorized to charge any fees or credit any overpayment to Deposit Account No. 02-2135.

Respectfully submitted,

By /Carolyn L. Greene/

Carolyn L. Greene
Attorney for Applicant
Registration No. 57,784
ROTHWELL, FIGG, ERNST & MANBECK
1425 K. Street, Suite 800
Washington, D.C. 20005
Telephone: (202) 783-6040